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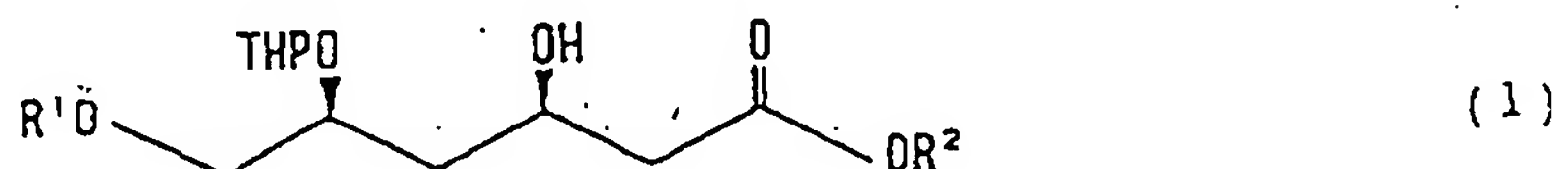
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(3R,5S)-3,5,6-trihydroxyhexanoic acid derivatives and methods for their production.

A (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative (1)



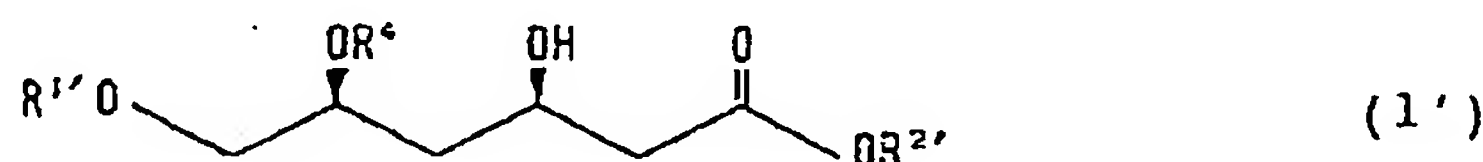
(R¹ = tert-butyl or benzyl; R² = C₁-C₄; THP = tetrahydropyranyl) is produced by enantioselectively hydrogenating an (S)-5,6-dihydroxy-3-oxohexanoic acid with a specific ruthenium-optically active phosphine complex as a catalyst. By this process the derivative (1) is easily and efficiently obtained under mild reaction conditions with a high selectivity for the syn-diol form. The derivative can easily be converted into a lactone moiety, which is the active part of an inhibitor of HMG-CoA reductase.

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The present invention relates to novel (3R,5S)-3,5,6-trihydroxyhexanoic acid derivatives useful as intermediates in the preparation of medicaments, and also to methods for their production.

Some of the optically active (3R,5S)-3,5,6-trihydroxyhexanoic acid derivatives having the specific configuration shown by the following formula (1')



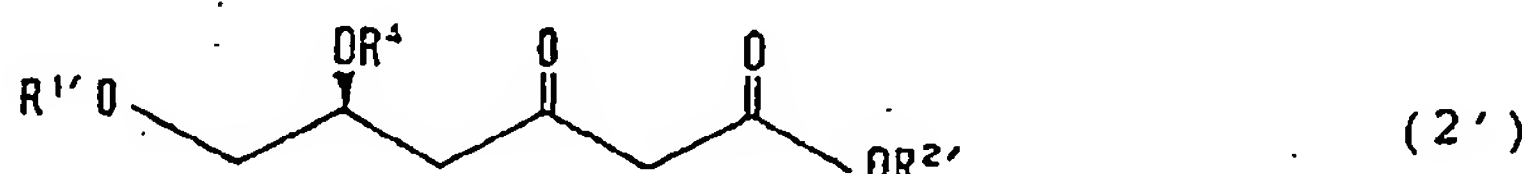
(wherein R^{1'} and R⁴ each represents a hydrogen atom or a protective group for a hydroxy group and R^{2'} represents an ester forming group), are already known compounds and it is reported that these compounds can be easily converted into lactone moieties having the chemical structure of, eg, campactin or mevinolin, which are regarded as having antihyperlipemic activity as described in K. Prasad et al., *Tetrahedron Lett.*, Vol. 25, No. 32, 3391-3394(1984). It is considered that the lactone moiety is the active part of an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (hereinafter referred to as "HMG-CoA") reductase, one of the predominant enzymes taking part in the increase of the concentration of cholesterol, which is the cause of hyperlipemia, and many analogs having the lactone moiety have been synthesized [J. R. Prous, *Drugs of the Future*, Vol. 12, No. 5, 437-442(1987)].

Many methods of synthesizing the (3R,5S)-3,5,6-trihydroxyhexanoic acid derivatives shown by the foregoing formula (1') have been reported. As a synthesis using as a starting material a compound having asymmetric carbon atoms at two sites, a synthetic method starting from D-glucose, which is a natural optically active compound, has been described by T. Lee, *Tetrahedron Lett.*, Vol. 26, No 41, 4995-4996(1985); however the method has the disadvantage that the reaction steps needed to obtain the desired compound are numerous.

Also, as a method of simultaneously introducing hydroxy groups at two sites in a syn-diol form, there is a method of obtaining a 3,5-dioxohexanoic acid derivative by reacting an acetoacetic acid derivative and an amide compound, and reducing the reaction product using sodium borohydride and an alkoxydialkylborane at a temperature from -70°C to -78°C; as described in JP-A-1-165547 (the term "JP-A" as used herein means an "unexamined published Japanese patent application") and T. Hanamoto et al., *Tetrahedron Lett.*, Vol. 29, No. 49, 6467-6470(1988); however by this method, a diastereomer only is achieved and not the desired optically active material.

Methods of forming asymmetric carbon atoms successively at two sites have been most widely utilized, and the following methods (a) to (g) have been reported.

(a) A method of obtaining an (S)-5,6-dihydroxy-3-oxohexanoic acid derivative shown by following formula (2')



(wherein R^{1'} and R⁴ each represents a hydrogen atom or a protective group for a hydroxy group and R^{2'} represents an ester forming group), from an (S)-3,4-dihydroxybutanoic acid ester derivative shown by following formula (5)



(wherein R^{1'} and R⁴ have the same meaning as above and R⁵ represents a hydrogen atom or an alkyl group), which has been synthesized from L-malic acid, which is a natural material. The foregoing hexanoic acid derivative (2') is then diastereo-selectively reduced using a reducing agent, such as a mixture of sodium borohydride and a trialkylborane or a mixture of sodium borohydride and an alkoxydialkylborane under a low temperature condition of about -70°C [European Patent - 0 244 364 A2, U.S. Patent 4,970,313, G. Wess et al., *Tetrahedron Lett.*, Vol. 31, No. 18, 2545-2548(1990), and K. Prasad et al., *Tetrahedron: Asymmetry*, Vol. 1, No. 5, 307-310(1990)].

(b) A method of obtaining the compound shown by foregoing formula (2') by reacting an optically active butyronitrile derivative and an α -haloacetic acid ester in the presence of zinc and diastereo-selectively reducing the reaction product as in method (a) described above (U.S. Patent 4,983,759).

(c) A method of synthesizing the compound shown by formula (2') from an optically active 3-hydroxypropionaldehyde derivative and diastereo-selectively reducing the synthesized product as in method (a) described above [M. Fukui et al., *Chem. Pharm. Bull.*, Vol. 38, No. 10, 2890-2892(1990)].

(d) A method of synthesizing the compound shown by formula (2') from 3-(3-methoxyphenyl)-2-propen-1-ol and then diastereo-selectively reducing the synthesized compound as in method (a) [D. A. Evans et al., *J. Org. Chem.*, Vol. 56, No. 2, 741-750(1991)].

In addition, the diastereo-selective reducing reaction of the compound shown by formula (2') common to the methods (a) to (d) is also reported in K. Chen et al., *Tetrahedron Lett.*, Vol. 28, No. 2, 155-158(1987), K. Chen et al., *Chemistry Lett.*, 1923-1926(1987), etc. Also, in F. G. Kathawala et al., *Helv. Chim. Acta*, Vol. 69, 803-805(1986), the diastereo-selectivities for the compound shown by foregoing formula (1') obtained in the case of using sodium borohydride and a trialkylborane, ferrous chloride, zinc borohydride, etc., for the diastereo-selective reducing reaction of the compound shown by formula (2') are compared. Furthermore, it is reported that, in respect of compounds of the formula (1') having an allyl group or a cyano group in place of the hydroxy group at the 6-position (which are compounds analogous to the compounds of formula (1')), by applying the diastereo-selective reducing reaction to the substrate obtained by carrying out, for example, an asymmetric aldol condensation of the aforesaid compound, and then optically resolving the reaction product, a corresponding optically active 3,5-dihydroxyhexanoic acid derivative can be obtained (J. E. Lynch et al., *Tetrahedron Lett.*, Vol. 28, No. 13, 1385-1388(1987); N. Balasubramanian et al., *J. Med. Chem.*, Vol. 32, No. 9, 2038-2041(1989); S. Y. Sit et al., *J. Med. Chem.*, Vol. 33, No. 11, 2982-2999(1990), and U.S. Patent 5,003,080].

(e) A method of obtaining the compound shown by formula (2') by reacting the dianion of acetoacetic acid ester with aldehyde, and reducing the obtained compound by reaction using sodium borohydride in absolute ethanol under ice-cooling (U.S. Patent 4,248,889).

(f) A method of obtaining the compound shown by formula (5) by ring-cleaving optically active 1-benzyloxy-2,3-epoxy-4-hydroxybutane and after introducing a protective group to the hydroxy group, oxidizing the product, and synthesizing by carrying out a Reformatsky reaction of the compound of formula (5) using ethyl bromoacetate and zinc [K. Prasad et al., *Tetrahedron Lett.*, Vol. 25, No. 32, 3391-3394(1984)].

(g) A method of reacting a (3R,5R)-5-amino-3-hydroxy-hexanoic acid derivative and a specific cyan compound $[\text{Na}_2\text{Fe}(\text{CN})_6\text{NO}]$ using potassium carbonate [G. J. McGarvey et al., *J. Org. Chem.*, Vol. 51, No. 20, 3913-3915(1986)].

However, the above-described methods have the following defects:-

Method (e) is a method of obtaining a racemic modification and the desired optically active substance cannot be obtained.

In method (f) it is difficult to obtain the optically active epoxide which is the raw material, and also the Reformatsky reaction does not have selectivity for the desired syn-diol form.

In method (g), it is difficult to obtain the raw material, and also the yield of the desired compound is low.

The diastereo-selective reducing reaction which is utilized for methods (a) to (d), which are most widely reported, is a method of inducing an asymmetric atom at another site by utilizing the asymmetric atom at one site and in methods (a) to (d), a desired compound can be obtained with a considerably high syn-diol form selectivity as compared with methods (e) to (g). However, in methods (a) to (d), the reaction must be carried out under a low temperature condition, whereby specific equipment is required in the case of synthesizing on an industrial scale; and also in these methods, an expensive reagent is required. Furthermore, in the method (a), L-malic acid, which is the raw material, is a very expensive compound.

In U.S. Patent No. 4,994,602 there is described a method of overcoming these drawbacks, comprising an enantioselective hydrogenation of a 4-tert-butoxyacetoacetic acid ester (which is a raw material that can be synthesized at a low cost) using a ruthenium-optically active phosphine complex as a catalyst to form an (S)-4-tert-butoxy-3-hydroxybutyric acid ester; reacting the butyric acid ester thus obtained and the lithium enolate of an acetic acid ester to provide an (S)-6-tert-butoxy-5-hydroxy-3-oxohexanoic acid ester; and obtaining the desired compound shown by formula (1') by diastereo-selectively enantioselectively hydrogenating the product thus obtained under mild temperature conditions using a ruthenium-optically active phosphine complex as a catalyst.

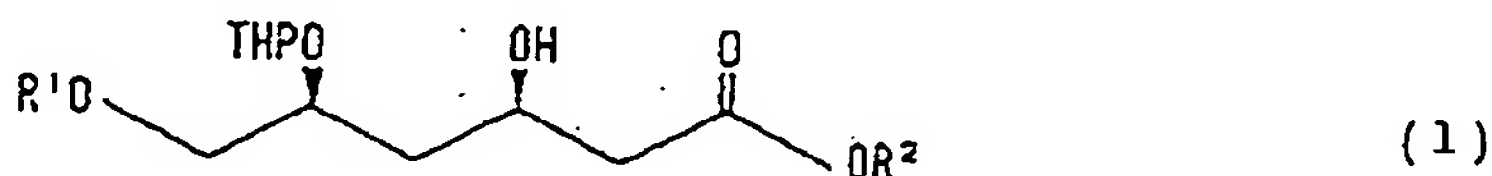
However, although this method overcomes the foregoing defects as regards the raw material and the reaction conditions, it is not sufficiently satisfactory as regards the diastereo-selectivity of the hydroxy group at the 3-position of the compound of formula (1'), as the value of from 60% d.e., to 82% d.e. in the compound obtained is not sufficiently high.

In addition, when carrying out the diastereo-selective reaction in the foregoing methods, R⁴ of the compound shown by formula (2') is a hydrogen atom in all cases. Accordingly, R⁴ of the compound shown by formula (1') obtained is also a hydrogen atom. In other methods, the compounds shown by formula (1') wherein R⁴ is a hydrogen atom or a protective group for a hydroxy group can be synthesized, but the protective groups for the hydroxy group practically disclosed are a 3-substituted silyl group and a phenylaminocarbonyl group only, which are reluctant to deprotect, requiring a very expensive reagent and severe reaction conditions.

Thus, there has been desired the development of a method of simply and efficiently obtaining a (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative, the hydroxy group at the 5-position of which can be easily deprotected.

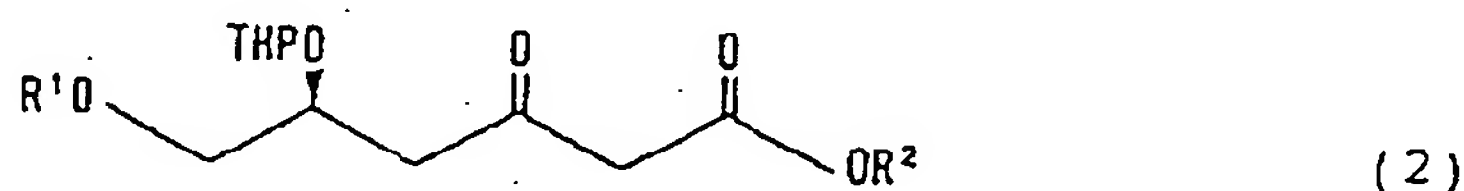
We have discovered that a novel compound, an (S)-5,6-dihydroxy-3-oxohexanoic acid derivative, the hydroxy group at the 5-position of which is protected with a tetrahydropyranyl group, can be obtained; and that, by enantio-selectively asymmetrically hydrogenating the foregoing compound using a specific ruthenium-optically active phosphine complex as a catalyst, there can also be obtained a novel compound, a (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative, the hydroxy group at the 5-position of which is protected with the tetrahydropyranyl group. This compound which is useful as an intermediate in the preparation of certain medicaments, can be easily and efficiently obtained under mild reaction conditions, at low cost and at a high stereoselectivity of 99.4 : 0.6 in the formation ratio of the syn-diol form : the anti-diol form.

According to one aspect of the present invention, there is provided a (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative represented by formula (1)



wherein R¹ represents a tert-butyl group or a benzyl group; R² represents a lower alkyl group; and THP represents a tetrahydropyranyl group.

Furthermore, according to another aspect of the present invention, there is provided a process of producing a (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative represented by the formula (1) described above, which comprises the step of enantioselectively hydrogenating an (S)-5,6-dihydroxy-3-oxohexanoic acid derivative represented by formula (2)

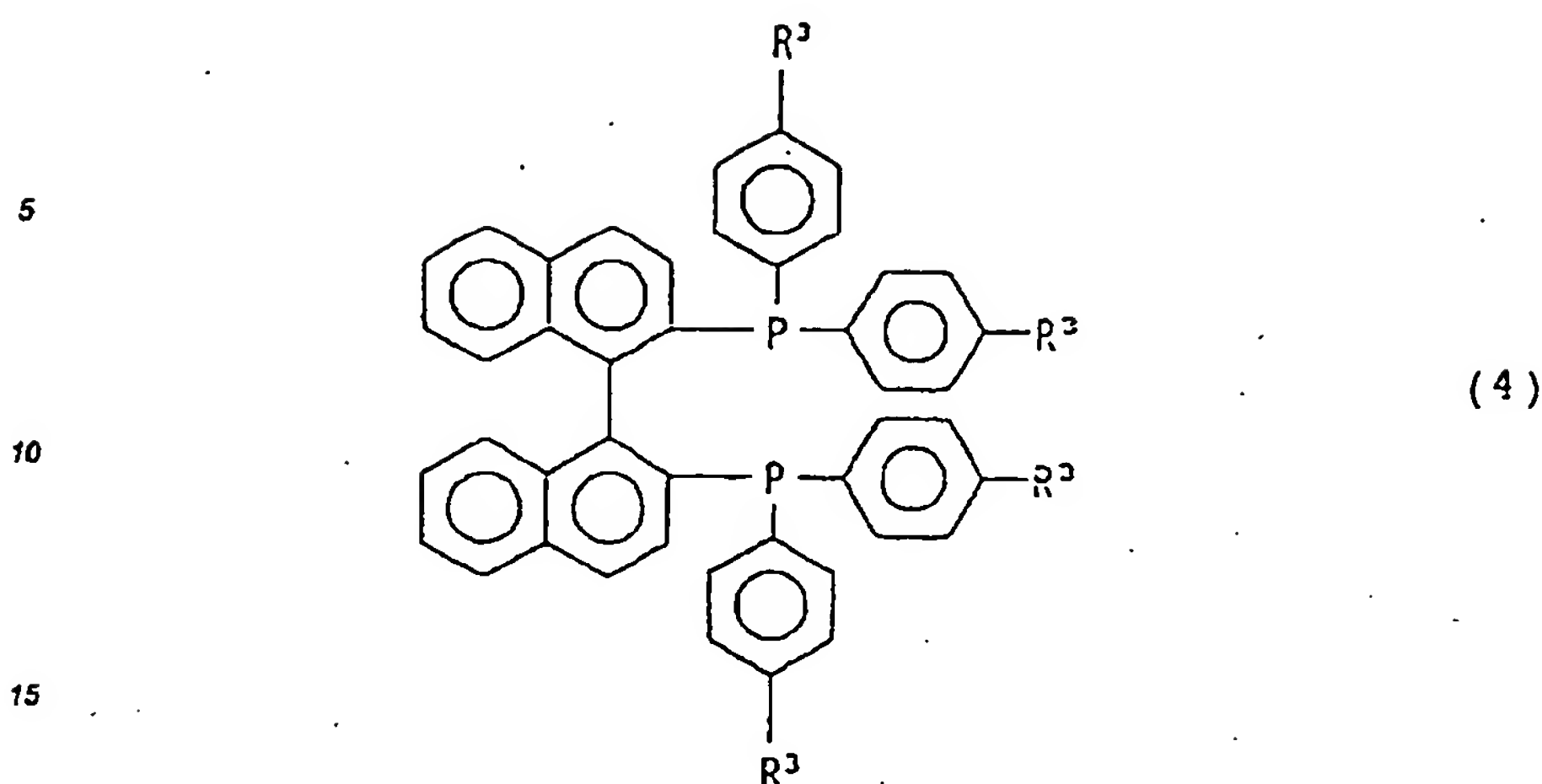


(wherein R¹, R², and THP have the same meaning as described above)

with a ruthenium-optically active phosphine complex represented by formula (3) as a catalyst:



wherein R³-BINAP represents a tertiary phosphine represented by formula (4)



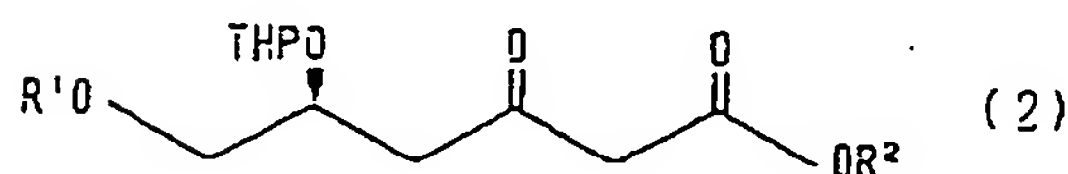
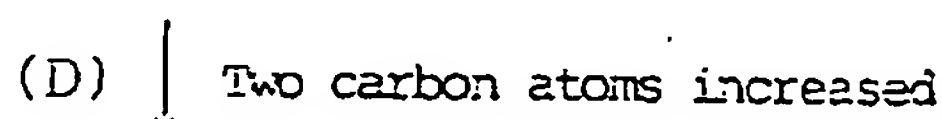
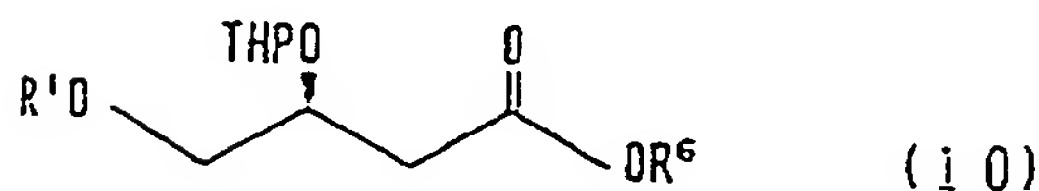
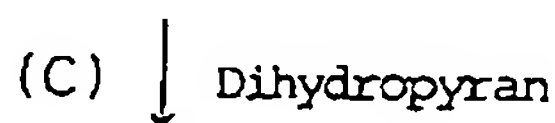
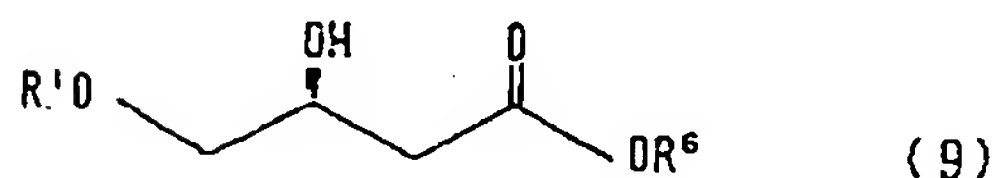
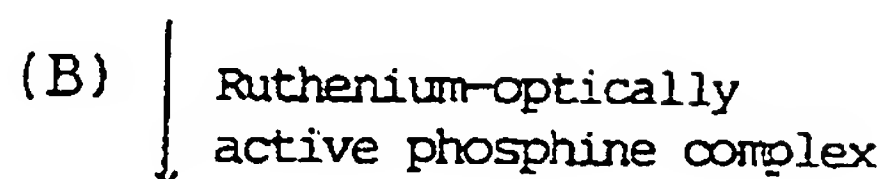
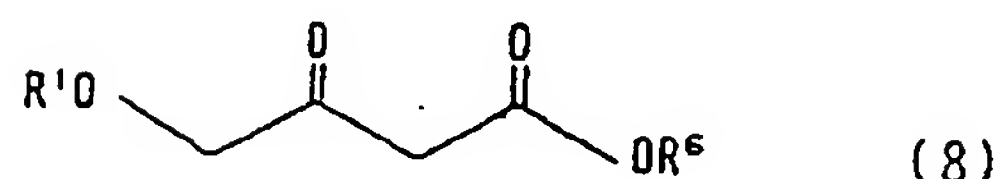
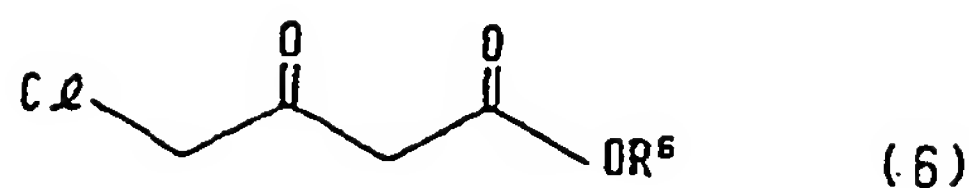
R^3 represents a hydrogen atom or a lower alkyl group; and X represents a chlorine atom or a bromine atom.

In the present invention, the term "lower alkyl group" means a straight chain or branched alkyl group having from 1 to 4 carbon atoms.

In the compound of formula (1), R^2 preferably is an ethyl group and tert-butyl group.

The (S)-5,6-dihydroxy-3-oxohexanoic acid derivative shown by formula (2) used as the raw material in the production method of the present invention is a novel compound having as a main feature that the hydroxy group at the 5-position is protected with a tetrahydropyranyl group. The derivative (2) is inexpensive as compared with the conventional compounds protected with a 3-substituted silyl group or a phenylaminocarbonyl group, and also has excellent syn-diol form selectivity when producing the (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative shown by formula (1) by the production method of the present invention. Furthermore, when it is necessary to deprotect the tetrahydropyranyl group, it can be easily deprotected under an acid condition, whereby the foregoing derivative of formula (1) can be converted into the original alcohol.

The compound shown by formula (2) can be obtained easily at a low cost and at a high optical purity by, for example, synthesizing the compound according to the following reaction scheme applied with the method described in U.S. Patent 4,994,602:



(In the above formulae, R¹, R², and THP have the same meaning as described above and R⁶ represents a lower alkyl group.)

(A) by reacting the easily commercial available 4-chloroacetoacetic acid ester shown by formula (6) and the alcohol shown by formula (7) by the method described in D. Seebach et al., *Synthesis*, 37-40(1986), the compound shown by formula (8) is obtained;

(B) then, by enantioselectively hydrogenating the compound of formula (8) using a ruthenium-optically active phosphine complex; Ru[(R)-R³-BINAP](O₂CR⁷)₂ (wherein R³-BINAP has the same meaning as described above and R⁷ represents a lower alkyl group or a trifluoromethyl group) obtained by the method described in U.S. Patent 4,739,084 or the ruthenium-optically active phosphine complex shown by foregoing formula (3) being used in the present invention as a catalyst according to the method described in U.S. Patent 4,933,482, the (S)-3,4-dihydroxybutanoic acid ester derivative shown by formula (9) is obtained;

(C) by reacting the compound shown by formula (9) and dihydropyran, the compound of formula (10) wherein the hydroxy group at the 3-position is protected with a tetrahydropyranyl group is obtained; and

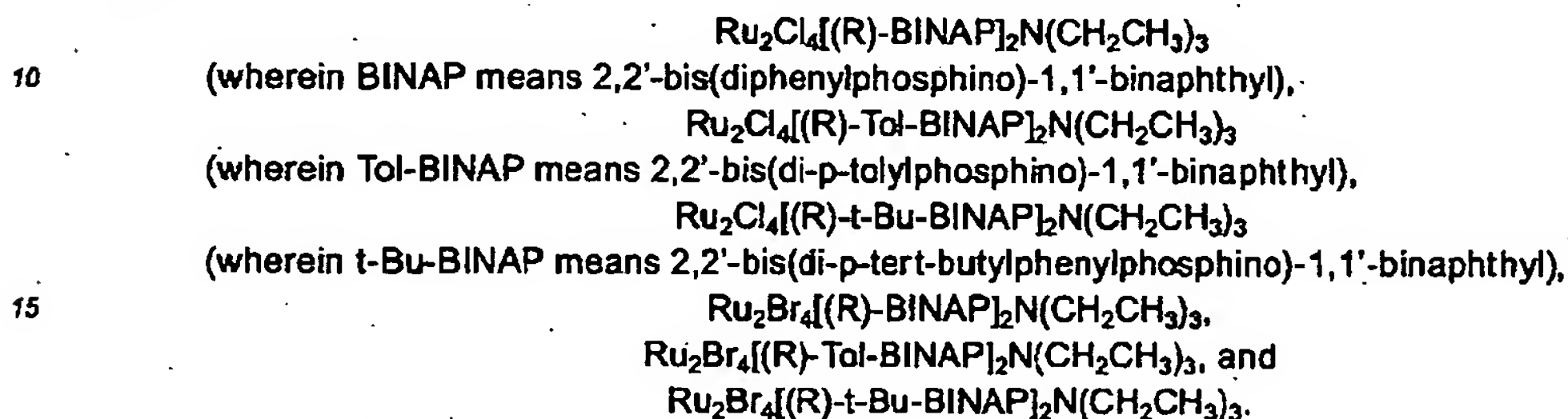
(D) after reacting the compound of formula (10) and the lithium enolate of an acetic acid ester by the method described in U.S. Patent 4,994,602 or after hydrolyzing the compound of formula (10) with an alkali such as sodium hydroxide, the reaction product or the hydrolyzed product is reacted with a malonic acid derivative such as potassium tert-butyl malonate, or potassium ethyl malonate, by applying the method described in U.S. Patent 5,003,080 to increase two carbon atoms, whereby the compound shown by formula (2) is obtained.

The ruthenium-optically active phosphine complex shown by formula (3) being used in the present inven-

tion can be obtained by the method described in U.S. Patent 4,691,037 or T. Ikariya et al., J. Chem. Soc., Chem. Commun., 922-924(1985).

That is, the complex shown by formula (3) is produced by reacting under heating $[RuX_2(COD)]_m$ (wherein m represents a natural number) obtained by reacting ruthenium halide (wherein the halogen is a chlorine atom or a bromine atom) and cycloocta-1,5-diene (hereinafter, is referred to as "COD") in ethanol and (R)-R³-BINAP in a solvent such as toluene, or ethanol, in the presence of triethylamine.

Specific examples of the ruthenium-optically active phosphine complex shown by formula (3) are as follows:



The production method of the present invention is as follows.

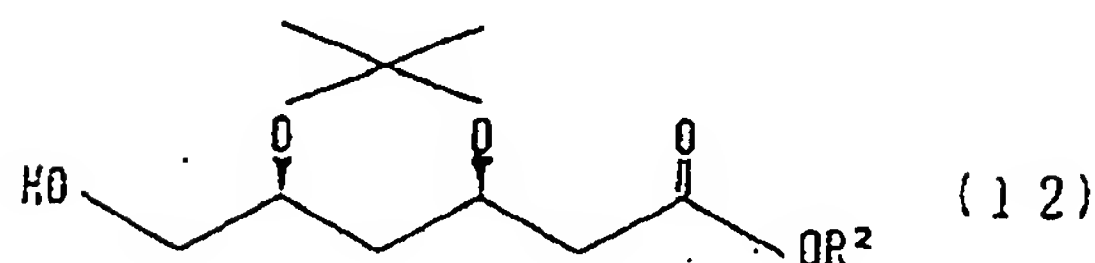
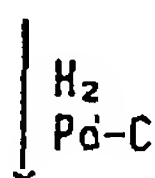
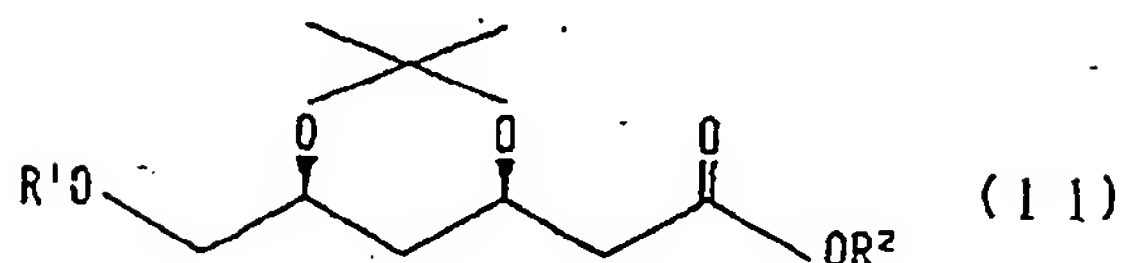
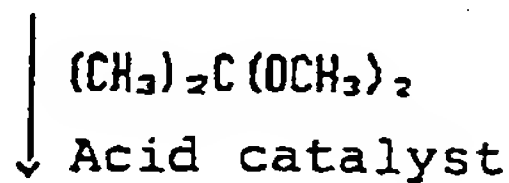
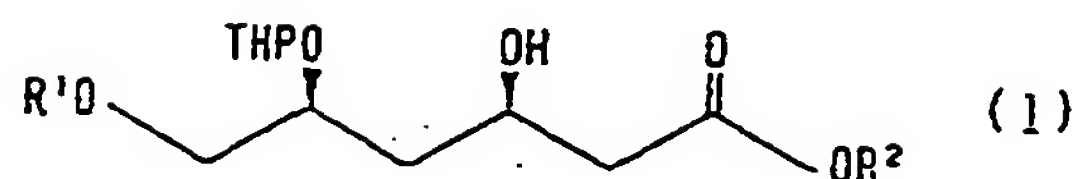
That is, the (S)-5,6-dihydroxy-3-oxohexanoic acid derivative shown by formula (2) is dissolved in an alcohol such as methanol, ethanol, iso-propanol, tert-butyl alcohol, etc., the ruthenium-optically active phosphine complex shown by formula (3) is added to the solution in an amount of from 0.0001 to 0.002 mol, and preferably from 0.0001 to 0.001 mol, per mol of the compound of formula (2), the hydrogenation is carried out under a hydrogen pressure of from 10 to 120 kg/cm², and preferably from 20 to 50 kg/cm² and at a reaction temperature of from 25 to 100°C, and preferably from 30 to 50°C. The solvent is removed by distillation, and the residue formed is purified by silica gel column chromatography to provide the desired (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative shown by formula (1).

The (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative shown by formula (1) thus obtained is a novel compound wherein the hydroxy group at the 5-position is protected with a tetrahydropyranyl group. Also, according to the production method of the present invention, the compound of formula (1) can be obtained easily at a low cost and with a high syn-diol form selectivity.

Also, the compound of formula (1) is excellent in the point that when it is necessary to deprotect the tetrahydropyranyl group in the case of using the compound as a raw material for synthesizing a medicament, the group can be easily deprotected.

In the method of the present invention, it sometimes happens that the compound wherein the hydroxy group at the 5-position is deprotected is by-produced in the step of the purification but the formation of such a compound has no influence on the foregoing syn-diol form selectivity.

Also, by carrying out the reaction shown below according to the method described, e.g., in U.S. Patent 4,970,313, the isopropylidene acetal, wherein the hydroxy groups at the 3-position and the 5-position are simultaneously protected, shown by formula (12) described below is obtained. The compound can be utilized in the synthesis of the active moiety of an inhibitor of HMG-CoA reductase, but in this case, the compound of formula (1) can be used for the reaction without releasing the tetrahydropyranyl group; and also, when the compound wherein the hydroxy group at the 5-position is deprotected is by-produced together with the compound shown by formula (1), they can be used for the reaction as the mixture thereof.



(in the above formulae, R_1 , R_2 , and THP have the same meaning as described above.)

EXAMPLES

The following Examples are intended to illustrate the present invention practically but not to limit it any way. In addition, the analyses in the Examples were carried out using the following analytical instruments.

Molecular Structure:

Infrared Absorption Spectrum (IR): Type IR-810 (trade name, made by JASCO Inc.)

Nuclear Magnetic Resonance Spectrum (NMR): Type AM-400 (400 MHz) (trade name, made by Bruker, Inc.)

Internal standard substance: Tetramethylsilane.

Optical Rotation: Type DIP-370 (trade name, manufactured by JASCO Inc.)

Optical Purity:

High-Performance Liquid Chromatography: Hitachi Liquid Chromatography L-6000 (trade name, manufactured by Hitachi Ltd.)

Column: Cosmosil 5SL, $\phi 4.6$ mm x 250 mm (trade name, manufactured by Nacalai Tesque Inc.)

Developing Solvent: Ether/hexane = 1/9 by volume (1 ml/min.)

Detector: UV Detector L-4000 (UV-254 nm) (trade name, manufactured by Hitachi, Ltd.)

Gas Chromatography: 5890A (trade name, manufactured by Hewlett-Packard Company)

Column: Neutra Bond 1 (trade name, manufactured by GL Sciences Inc.)

Temperature: 100 to 250°C (raised at 10°C/min.)

REFERENCE EXAMPLE 1**Production of Ethyl 4-Benzyloxyacetoacetate (8):**

5 In a 500 ml reaction flask were placed 8.0 g (0.2 mol) of sodium hydride and 150 ml of tetrahydrofuran, and then 10.8 g (0.1 mol) of benzyl alcohol of formula (7) described above was added dropwise to the suspension at a temperature of from 40 to 50°C under a nitrogen gas atmosphere. Thereafter, the resultant mixture was stirred for one hour and after adding dropwise 16.4 g (0.1 mol) of ethyl 4-chloroacetoacetate of formula (6) to the mixture, the reaction was carried out for 5 hours at room temperature. The reaction mixture obtained
10 was added to 50 ml of ice-water and the product formed was extracted with 200 ml of toluene. After drying the organic layer (extract) obtained, toluene and tetrahydrofuran were distilled off and then the residue was distilled to provide 14.16 g (0.06 mol, percent yield 60%) of ethyl 4-benzyloxyacetoacetate of formula (8) described above as a colorless transparent liquid.

Boiling Point: 135°C/1mmHg

15 IR(neat) cm^{-1} : 2975, 1740, 1730, 1660, 1500

$^1\text{H-NMR}(\text{CDCl}_3)$:

δppm : 1.24(t,3H,J=7.2Hz), 3.55(s,2H),
4.16(s,2H), 4.20(q,2H,J=7.2Hz),
4.55(s,2H), 7.33(aromatic,5H)

REFERENCE EXAMPLE 2**Production of Ethyl (S)-4-Benzyloxy-3-hydroxybutyrate (9):**

25 In a 100 ml autoclave previously displaced with a nitrogen gas was placed 4.72 g (20.0 mmol) of ethyl 4-benzyloxyacetoacetate of formula (8) obtained in Reference Example 1 and after adding thereto a solution of 35 mg (0.02 mmol) of $\text{Ru}_2\text{Cl}_4[(\text{R})\text{-Tol-BINAP}]_2\text{N}(\text{CH}_2\text{CH}_3)_3$ dissolved in 0.1 ml of methylene chloride together with 3.7 ml of ethanol, the enantioselective hydrogenation reaction was carried out under a hydrogen pressure of 10 to 11 kg/cm^2 , and at a reaction temperature of 100°C for 2 hours with stirring. After the reaction was over,
30 the solvent was distilled off and the residue formed was distilled to provide 4.24 g (17.8 mmol, percent yield 89%) of ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) described above.

Boiling Point: 124°C/0.3mmHg

$[\alpha]_D^{25}(c=1.1, \text{CHCl}_3)$: -11.5°

IR(neat) cm^{-1} : 3450, 2975, 1740, 1500

35 $^1\text{H-NMR}(\text{CDCl}_3)$:

δppm : 1.24(t,3H,J=7.1Hz),
2.55(d,2H,J=6.3Hz), 3.50(m,2H),
4.17(q,2H,J=7.1Hz), 4.24(m,1H),
4.68(s,2H), 7.32(aromatic, 5H)

40 The ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) obtained in the above step was reacted with (R)-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (hereinafter, is referred to as "MTPA") in methylene chloride in the presence of N,N'-dicyclohexylcarbodiimide and a catalytic amount of 4-dimethylaminopyridine to synthesize an MTPA ester form. As the result of analyzing the product by high-performance liquid chromatography (hereinafter, is referred to as "HPLC"), it was confirmed that the product was a mixture of 99.15%
45 ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) and 0.85% ethyl (R)-4-benzyloxy-3-hydroxybutyrate. Also, the optical purity of ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) was 98.3%e.e.

REFERENCE EXAMPLE 3**Production of Ethyl (S)-4-Benzyloxy-3-tetrahydropyranyloxy-butyrate (10):**

To 4.0 g (16.7 mmol) of ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) obtained in Reference Example 2 was added 20 ml of toluene and after further adding thereto 5 mg (26.3 mmol) of p-toluenesulfonic acid monohydrate, 1.6 g (19.0 mmol) of 3,4-dihydropyran was added dropwise to the mixture at room temperature followed by carrying out the reaction for 2 hours at the same temperature. The reaction mixture obtained
55 was washed twice with 5 ml of an aqueous solution of sodium hydrogencarbonate and dried. After distilling off the solvent from the product, the residue was purified by silica gel column chromatography (developing solvent: hexane/ethylacetate = 9/1 by volume) to provide 4.83 g (15.0 mol, percent yield 90%) of ethyl-(S)-4-benzyloxy-

3-tetrahydropyranyloxybutyrate shown by formula (10) described above as a colorless transparent liquid.

IR(neat) cm^{-1} : 2940, 1735, 1500, 1030, 740, 700

$^1\text{H-NMR}(\text{CDCl}_3)$:

δppm : 1.24(dt, 3H, $J=2.1\text{Hz}, 7.2\text{Hz}$),
 1.43-1.84(m, 6H), 2.62(m, 2H),
 3.46(m, 1H), 3.54(d, 1H, $J=5.0\text{Hz}$),
 3.84(m, 1H), 4.10(dq, 2H, $J=2.1\text{Hz}, 7.2\text{Hz}$),
 4.30(m, 1H), 4.54(d, 2H, $J=2.1\text{Hz}$),
 4.78(m, 1H), 7.32(aromatic, 5H)

REFERENCE EXAMPLE 4

Production of Ethyl (S)-6-Benzoyloxy-5-tetrahydropyranyloxy-3-oxohexanoate (2):

In 20 ml of methanol were dissolved 4.8 g (14.9 mmol) of ethyl (S)-4-benzyloxy-3-tetrahydroxypranyloxybutyrate of formula (10) obtained in Reference Example 3 and 0.656 g (16.4 mmol) of sodium hydroxide and the solution was refluxed for 2 hours. After distilling off methanol from the reaction mixture, 20 ml of ice-water was added to the residue and the mixture was extracted with 30 ml of toluene. The aqueous layer was recovered and acidified with 1N sulfuric acid with cooling until pH became 6, the product was extracted with 50 ml of ethyl acetate. The organic layer (the extract) obtained was dried and concentrated, and the residue was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate = 95/5 by volume) to provide 4.12 g (14.0 mmol, percent yield 94%) of (S)-4-benzyloxy-3-tetrahydropyranyloxybutyric acid as a light yellow transparent liquid.

IR(neat) cm^{-1} : 3400-3500, 2950, 1715, 1600

Then, 4.0 g (13.6 mmol) of (S)-4-benzyloxy-3-tetrahydropyranyloxybutyric acid obtained was dissolved in 30 ml of tetrahydrofuran and then 2.75 g (16.9 mmol) of 1,1'-carbonyldiimidazole was added to the solution at -15°C . Then, the mixture was stirred for one hour to increase a temperature to room temperature. The mixture was added dropwise to a suspension of 2.80 g (29 mmol) of magnesium chloride, 2.9 g (29 mmol) of triethylamine, and 4.22 g (25 mmol) of potassium ethyl malonate in 30 ml of tetrahydrofuran and the reaction was carried out for 6 hours at room temperature.

The reaction mixture obtained was concentrated and after adding thereto 1 N sulfuric acid until pH became 6 while cooling with the addition of 20 ml of ice-water, the product was extracted with 50 ml of ethyl acetate. The organic layer (the extract) was recovered, dried, and concentrated. The residue formed was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate = 9/1 by volume) to provide 3.80 g (10.43 mmol) of ethyl (S)-6-benzyloxy-5-tetrahydropyranyloxy-3-oxohexanoate of formula (2) described above as a colorless transparent liquid with a percent yield of 70% from ethyl (S)-4-benzyloxy-3-tetrahydropyranyloxybutyrate of formula (10).

IR(neat) cm^{-1} : 2950, 1740-1720, 1650, 1500, 1150

$^1\text{H-NMR}(\text{CDCl}_3)$:

δppm : 1.26(t, 3H, $J=7.2\text{Hz}$), 1.50-1.80(br, 6H),
 2.80(m, 2H), 3.45-3.5(m, 4H),
 4.26(q, 2H, $J=7.2\text{Hz}$), 4.52(s, 2H),
 7.34(aromatic, 5H)

REFERENCE EXAMPLE 5

Production of tert-Butyl (S)-6-Benzoyloxy-5-tetrahydropyranyloxy-3-oxohexanoate (2):

In a 200 ml reaction flask was placed 40 ml of tetrahydrofuran and after cooling the flask in ice-water to 0°C , 60 ml of a n-hexane solution of 1.6M of lithium diisopropylamide was added thereto and further a solution of 11.06 g (95.4 mmol) of tert-butyl acetate dissolved in 10 ml of tetrahydrofuran was added dropwise to the mixture. Thereafter, the resultant mixture was stirred for 30 minutes, and after cooling the reaction mixture to -20°C , a solution of 12.3 g (33.8 mmol) of ethyl (S)-6-benzyloxy-5-tetrahydropyranyloxy-3-oxohexanoate of formula (2) dissolved in 20 ml of a tetrahydrofuran solution was added dropwise to the reaction mixture. Thereafter, the resultant mixture was stirred for one hour, the reaction mixture was poured into 100 ml of a saturated aqueous solution of ammonium chloride and the product was extracted with ethyl acetate. After drying the organic layer (the extract) obtained, the solvent was distilled off and the residue formed was purified by silica gel column chromatography (developing solvent: hexane/ethyl acetate = 95/5 by volume) to provide 9.46 g (24.1

mmol, percent yield 71%) of tert-butyl (S)-6-benzyloxy-5-tetrahydropyranyloxy-3-oxohexanoate of formula (2) as a light-yellow transparent liquid.

IR(neat) cm^{-1} : 2950, 1740-1720, 1650, 1500, 1150

$^1\text{H-NMR}(\text{CDCl}_3)$:

5 δppm : 1.47(9H), 1.50-1.80(6H), 2.80(m,2H),
3.45-3.5(m,4H), 4.52(s,2H),
7.34(aromatic,5H)

EXAMPLE 1

Production of Ethyl (3R,5S)-6-Benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate (1):

After dissolving 1.0 g (2.75 mmol) of ethyl (S)-6-benzyloxy-5-tetrahydropyranyloxy-3-oxohexanoate of formula (2) obtained in Reference Example 4 in 2.0 ml of ethanol, the solution thus formed was placed in a 100 ml autoclave previously displaced with a nitrogen gas. Then, after adding thereto a solution of 2.3 mg (0.0013 mmol) of $\text{Ru}_2\text{Cl}_4[(\text{R})\text{-Tol-BINAP}]_2\text{N}(\text{CH}_2\text{CH}_3)_3$ of formula (3) dissolved in 0.1 ml of methylene chloride, the enantioselective hydrogenation reaction was carried out for 18 hours with stirring under a hydrogen pressure of 30 kg/cm² and at a reaction temperature of 35°C.

After the reaction was over, the solvent was recovered and the residue formed was purified by silica gel column chromatography (developing solvent: n-hexane/ethyl acetate = 85/15 by volume) while simultaneously removing the catalyst to provide 320 mg (0.87 mmol, percent yield 32%) of ethyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate shown by formula (1) described above as a colorless transparent liquid.

IR(neat) cm^{-1} : 3450, 2940, 1730, 1600, 1100, 740, 700

$^1\text{H-NMR}(\text{CDCl}_3)$:

25 δppm : 1.28(t,3H,J=7.2Hz), 1.60-1.80(m,6H),
2.40(m,2H), 3.40(t,2H,J=5.6Hz),
3.50(m,2H), 3.65(m,1H), 4.18(m,2H),
4.25(q,2H,J=7.2Hz), 4.54(s,2H),
30 7.32(aromatic,5H)

Then, ethyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) thus obtained was reacted with MTPA to form an ester form as in Reference Example 2 and as the result of analyzing by HPLC, it was confirmed that the optical purity of the product was higher than 99% ee.

In addition, during the purification of ethyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate, 209 mg (0.75 mmol, percent yield 27%) of ethyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate without having the tetrahydropyranyl group as the protective group for the hydroxy group at the 5-position was obtained as a white crystal and the total yield of the foregoing compound and ethyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) was 59%.

Melting Point: 34-35 °C

40 IR(KBr) cm^{-1} : 3400, 2900, 1720, 1600, 735, 700

$^1\text{H-NMR}(\text{CDCl}_3)$:

45 δppm : 1.26 (t,3H,J=7.2 Hz), 1.65 (m,2H),
2.46 (m,2H), 3.40 (m,2H), 4.08 (m,1H),
4.18 (q,2H,J=7.2 Hz), 4.29 (m,1H),
4.55 (s,2H), 7.32(aromatic,5H)

When ethyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate thus obtained was reacted with acetone dimethylacetal to form isopropylidene acetal and as the result of analyzing by gas chromatography, it was confirmed that the formation ratio of the syn-diol form/the anti-diol form was 99/1 by weight and the selectivity for the syn-diol form was 98% d.e.

Also, when ethyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate was recrystallized from ethanol and the analysis was carried out by the same manner as above, it was confirmed that the formation ratio of the syn-diol form/the anti-diol form was 99.4/0.6 by weight and the selectivity for the syn-diol form was 98.8% d.e.

In addition, for the sake of comparison, the compound, ethyl (3R,5S)-6-benzyloxy-5-tert-butyldimethylsilyloxy-3-hydroxyhexanoate wherein a tert-butyldimethylsilyl group, which was a conventionally known 3-substituted silyl group, was introduced in place of the tetrahydropyranyl group as the protective group for the hydroxy group at the 5-position in foregoing formula (1) was synthesized.

That is, when the foregoing enantioselective hydrogenation was carried out by the same reaction conditions as above except that ethyl (S)-6-benzyloxy-5-tert-butyldimethylsilyloxy-3-oxohexanoate was used in

place of ethyl (S)-6-benzyloxy-5-tetrahydropyranyloxy-3-oxohexanoate of formula (2), a mixture of ethyl (3R,5S)-6-benzyloxy-5-tert-butyldimethylsilyloxy-3-hydroxyhexanoate and ethyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate without having the tert-butyldimethylsilyl group was obtained. The product mixture was induced to isopropylidene acetal as described above and as the result of analyzing by gas chromatography, it was confirmed that the formation ratio of the syn-diol form/the anti-diol form was 96/4 by weight and the selectivity for the syn-diol form was 92% d.e.

From the foregoing results, it can be seen that when the reactions are carried out under the same conditions, the compound of the present invention is obtained at about 6% higher selectivity in the diastereomer excess ratio than in the case of the compound having introduced thereto the conventional protective group. The difference in the selectivity for the syn-diol form means that the compound of the present invention is excellent, particularly, in the synthesis of a medicament.

In addition, ethyl (S)-6-benzyloxy-5-tert-butyldimethylsilyloxy-3-oxohexanoate described above was obtained as follows.

That is, ethyl (S)-4-benzyloxy-3-hydroxybutyrate of formula (9) obtained in Reference Example 2 was reacted with tert-butyldimethylsilyl chloride in a mixed solvent of ethyl acetate and toluene at 1 : 1 by volume in the presence of 1 equivalent of imidazole and a catalytic amount of 4-dimethylaminopyridine to provide ethyl (S)-4-benzyloxy-3-tert-butyldimethylsilyloxyacetate, and then by increasing two carbon atoms according to the method described in Reference Example 4, desired ethyl (S)-6-benzyloxy-5-tert-butyldimethylsilyloxy-3-oxohexanoate was obtained.

EXAMPLE 2

Production of tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate (1):

In 2.0 ml of methanol was dissolved 1.0 g (2.55 mmol) of tert-butyl (S)-6-benzyloxy-3-oxo-5-tetrahydropyranyloxyhexanoate of formula (2) obtained in Reference Example 5 and the enantioselective hydrogenation reaction was carried out as in Example 1 using $\text{Ru}_2\text{Cl}_4[(\text{R})\text{-Tol-BINAP}]_2\text{N}(\text{CH}_2\text{CH}_3)_3$ of formula (3) for 18 hours with stirring under a hydrogen pressure of 30 kg/cm² and at a reaction temperature of from 35 to 40°C. After the reaction was over, the solvent was recovered and the residue formed was purified by silica gel column chromatography (developing solvent: n-hexane/ethyl acetate = 85/15 by volume) to provide 350 mg (0.89 mmol, percent yield 35%) of tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) as a colorless transparent liquid.

IR(neat) cm⁻¹: 3450, 2950, 1730, 1600, 1100, 740, 700

¹H-NMR(CDCl₃):

δppm: 1.60(s,9H), 1.60-1.80(m,6H),
2.40(m,2H), 3.40(t,2H,J=5.6Hz),
3.50(m,2H), 3.65(m,1H), 4.18(m,2H),
4.54(s,2H), 7.32(aromatic,5H)

Then, tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) obtained was reacted with MTPA to form an ester form as in Reference Example 2 and as the result of analyzing by HPLC, it was confirmed that the optical purity of the product was higher than 95%e.e.

In addition, during the purification of tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate, 280 mg (0.90 mmol, percent yield 35%) of tert-butyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate without having the tetrahydropyranyl group as the protective group for the hydroxy group at the 5-position was obtained as a colorless transparent liquid and the total yield of the foregoing compound and tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) was 70%.

IR(neat) cm⁻¹: 3450, 2900, 1720, 1600, 735, 700

¹H-NMR(CDCl₃):

δppm: 1.60(Br,9H), 1.65(m,2H), 2.45(m,2H),
3.40(m,2H), 4.08(m,1H), 4.29(m,1H),
4.55(s,2H), 7.32(aromatic,5H)

When tert-butyl (3R,5S)-6-benzyloxy-3,5-dihydroxyhexanoate obtained was reacted with acetone dimethyl acetal to form isopropylidene acetal and as the result of analyzing by gas chromatography, it was confirmed that the formation ratio of the syn-diol form/the anti-diol form was 91/9 by weight and the selectivity for the syn-diol form was 82% d.e.

EXAMPLE 3

Production of tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate (1):

5 In 4.0 ml of tert-butyl alcohol was dissolved 2.0 g (5.10 mmol) of tert-butyl (S)-6-benzyloxy-3-oxo-5-tetrahydropyranyloxyhexanoate of formula (2) obtained in Reference Example 5 and the solution was placed in a 100 ml autoclave previously displaced with a nitrogen gas. Then, after adding thereto a solution of 4.6 mg (0.0026 mmol) of $\text{Ru}_2\text{Cl}_4[(\text{R})\text{-Tol-BINAP}]_2\text{N}(\text{CH}_2\text{CH}_3)_3$ of formula (3) dissolved in 0.15 ml of methylene chloride, the enantioselective hydrogenation reaction was carried out for 18 hours with stirring under a hydrogen pressure of 30 kg/cm² and at a reaction temperature of 45°C. The conversion was 95%.

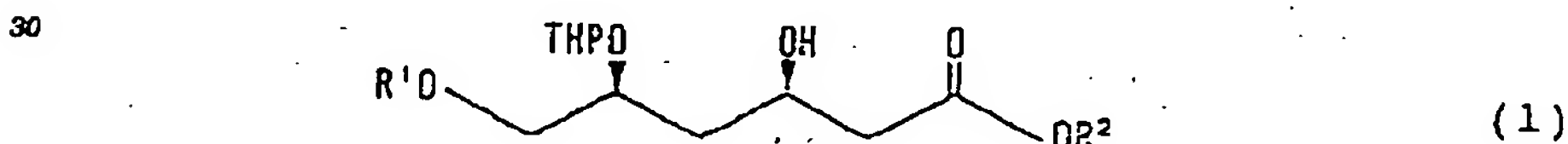
10 After the reaction was over, the solvent was recovered and the residue was purified by silica gel column chromatography (developing solvent: n-hexane/ethyl acetate = 85/15 by volume) while simultaneously removing the catalyst to provide 1.2 g (3.05 mmol, percent yield 60%) of tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) described above as a colorless transparent liquid.

15 Then, tert-butyl (3R,5S)-6-benzyloxy-3-hydroxy-5-tetrahydropyranyloxyhexanoate of formula (1) obtained was reacted with acetone dimethyl acetal to form isopropylidene acetal and as the result of analyzing by gas chromatography, it was confirmed that the formation ratio of the syn-diol form/the anti-diol form was 90/10 by weight and the selectivity of the syn-diol form was 80% d.e.

20 As described above, according to the present invention, the (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative which is a useful compound capable of being easily converted into a lactone moiety, which is the active part of an inhibitor of HMG-CoA reductase, can be easily and efficiently obtained under a mild reaction condition with a high selectivity for the syn-diol form.

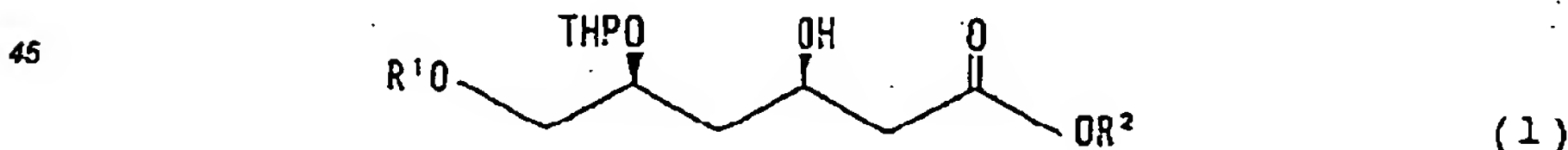
25 Claims

1. A (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative represented by formula (1)

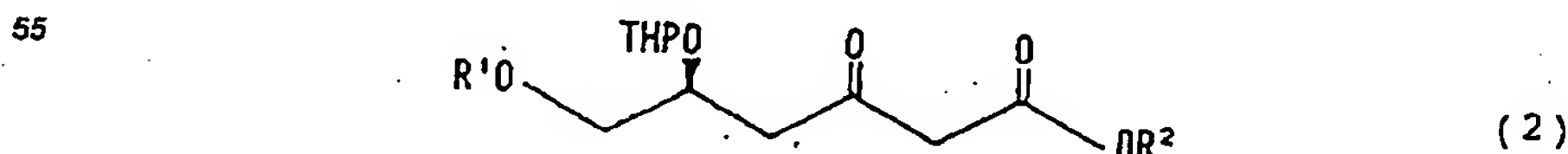


35 wherein R¹ represents a tert-butyl group or a benzyl group; R² represents a lower alkyl group; and THP represents a tetrahydropyranyl group.

2. A (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative as claimed in claim 1, wherein R² is an ethyl group.
- 40 3. A (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative as claimed in claim 1, wherein R² is a tert-butyl group.
4. A method of producing a (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative represented by formula (1)



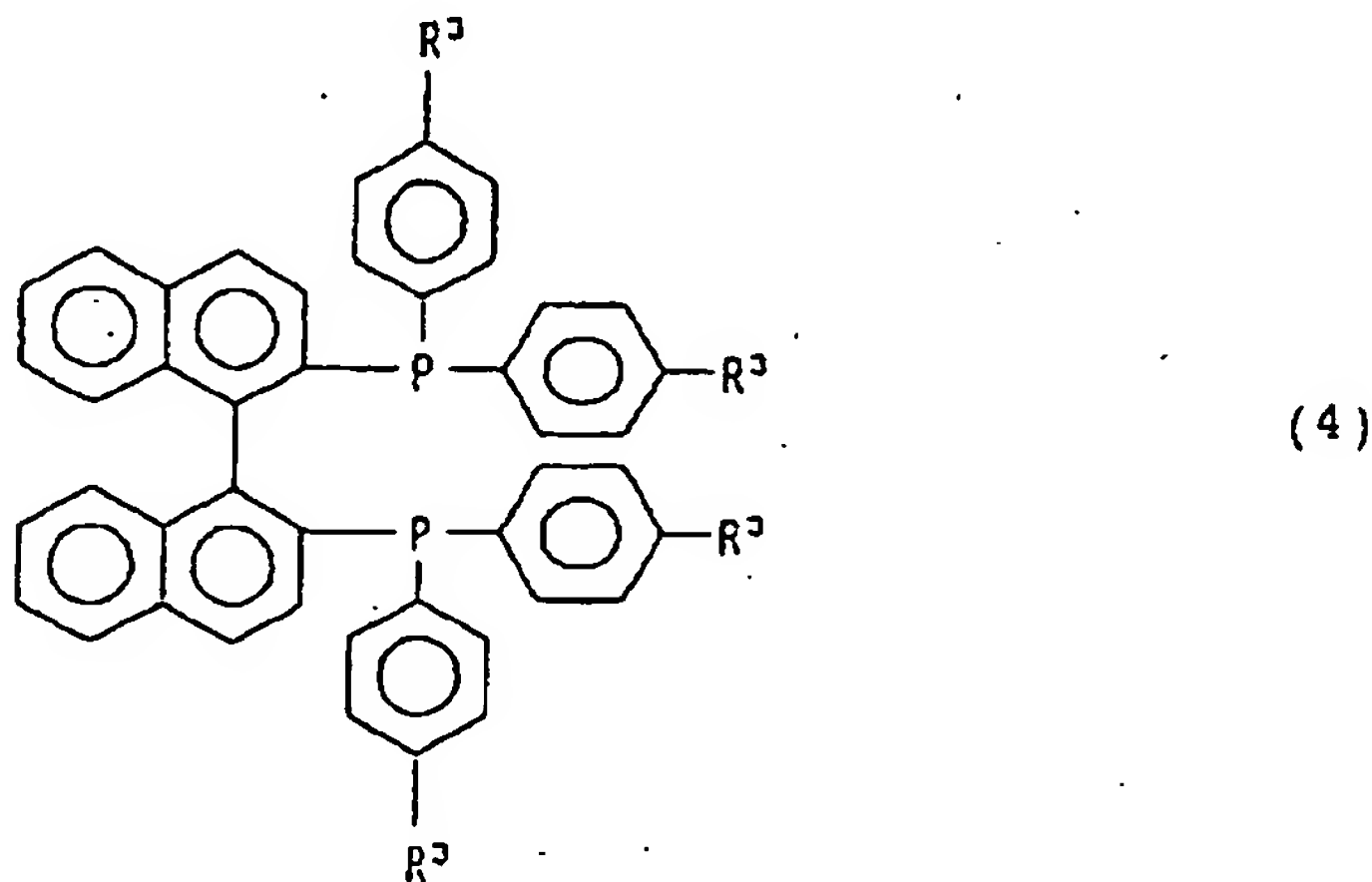
50 wherein R¹ represents a tert-butyl group or a benzyl group; R² represents a lower alkyl group; and THP represents a tetrahydropyranyl group, which comprises the step of enantioselectively hydrogenating an (S)-5,6-dihydroxy-3-oxohexanoic acid derivative represented by formula (2)



wherein R^1 , R^2 , and THP have the same meaning as described above,
with a ruthenium-optically active phosphine complex represented by formula (3) as a catalyst

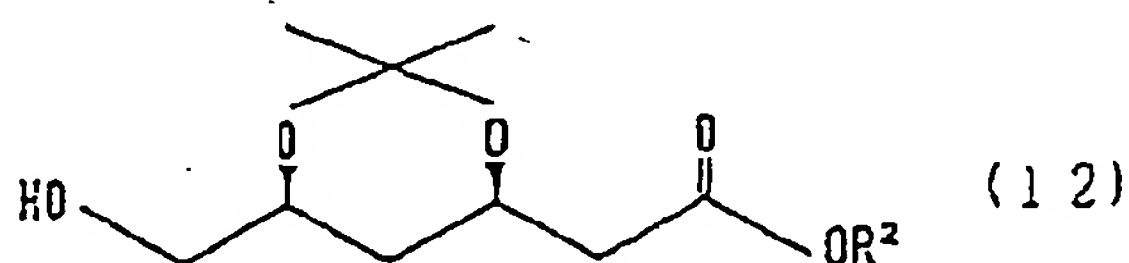


wherein R^3 -BINAP represents a tertiary phosphine represented by formula (4)



wherein R^3 represents a hydrogen atom or a lower alkyl group; and X represents a chlorine atom or a bromine atom.

5. A method as claimed in claim 4, wherein the trihydroxyhexanoic acid derivative represented by formula (1) is subsequently reacted with 2,2-dimethoxypropane in the presence of an acid catalyst and then hydrogenated to produce a compound of the following formula (12)



wherein R^2 has the previous significance.



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⑫

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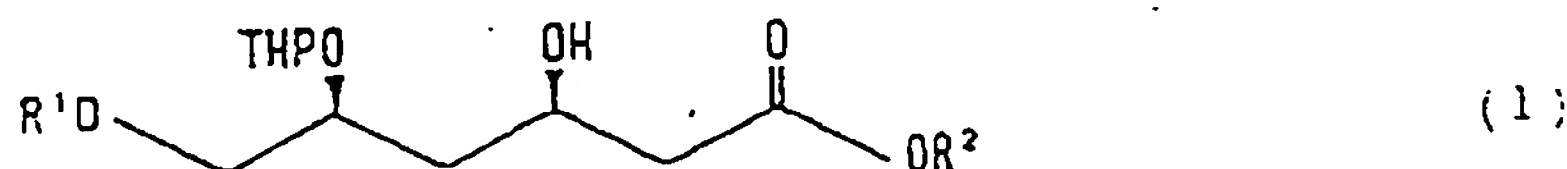
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⑤ (3R,5S)-3,5,6-trihydroxyhexanoic acid derivatives and methods for their production.

⑤ A (3R,5S)-3,5,6-trihydroxyhexanoic acid derivative (1)



(R¹ = tert-butyl or benzyl; R² = C₁-C₄; THP = tetrahydropyranyl) is produced by enantioselectively hydrogenating an (S)-5,6-dihydroxy-3-oxohexanoic acid with a specific ruthenium-optically active phosphine complex as a catalyst. By this process the derivative (1) is easily and efficiently obtained under mild reaction conditions with a high selectivity for the syn-diol form. The derivative can easily be converted into a lactone moiety, which is the active part of an inhibitor of HMG-CoA reductase.

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European Patent
Office

EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	EP-A-0 385 733 (TAKASAGO INTERNATIONAL CORPORATION) * claims *	1,4	C07D319/06 C07D309/12
Y	EP-A-0 374 922 (KANEGAFUCHI CHEMICAL INDUSTRY CO., LTD) * claims 1-7 *	1,4	
A	* claims 8,9,11 *	5	
D,A	EP-A-0 319 847 (HOECHST AKTIENGESELLSCHAFT) * claims *	1-5	
D,A	TETRAHEDRON LETTERS. vol. 31, no. 18, 1990, OXFORD GB pages 2545 - 2548 G.WESS ET AL 'Stereoselective synthesis of HR 780 a new highly potent hmg-coa reductase inhibitor' * the whole document *	1-5	
A	HETEROCYCLES vol. 24, no. 8, 1986, TOKYO pages 2173 - 2175 TSUGUO SATO ET AL 'Synthesis of parasorbic acid, the component of sorbus aukuparia l.' * the whole document *	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25 February 1994	Examiner Henry, J
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EP 0 583 171 A3 (PCT/CH)